A COMPARATIVE STUDY OF INTRATHECALLY ADMINISTERED MIDAZOLAM AND FENTANYL IN COMBINATION WITH BUPIVACAINE FOR INTRAOPERATIVE COMFORT AND POSTOPERATIVE ANALGESIA

A STUDY OF 120 CASES

DISSERTATION SUBMITTED FOR THE DEGREE OF DOCTOR OF MEDICINE BRANCH X - ANAESTHESIOLOGY

SEPTEMBER 2006

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI.

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CERTIFICATE

This to certify that this dissertation entitled **A COMPARITIVE STUDY OF INTRATHECALLY ADMINISTERED MIDAZOLAM AND FENTANYL IN COMBINATION WITH BUPIVACAINE FOR INTRAOPERATIVE COMFORT AND POSTOPERATIVE ANALGESIA** is a bonafide record of work done by dr.c.vairavarajan, under my guidance and supervision in the Department of Anaesthesiology, Madurai Medical College, Madurai, during the period of his postgraduate study for M.D.ANAESTHESIOLOGY from 2003 to 2006.

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DECLARATION

I, Dr.C.Vairavarajan solemnly declare that the dissertation titled, **A COMPARITIVE STUDY OF INTRATHECALLY ADMINISTERED MIDAZOLAM AND FENTANYL IN COMBINATION WITH BUPIVACAINE FOR INTRAOPERATIVE COMFORT AND POSTOPERATIVE ANALGESIA** has been prepared by me at Department of Anaesthesiology, Madurai Medical College, Madurai in partial fulfillment of the regulation for the award of M.D. Anaesthesiology degree examination of the Tamil Nadu Dr.M.G.R. Medical University., Chennai to be held in September 2006.

MADURAI
10-04-2006

ACKNOWLEDGEMENT

I am deeply indebted to **Dr.S.Subbiah** M.N.A.M.S, D.A., M.D., D.C.H., Professor and Head of the Department of Anaesthesiology, Madurai Medical College, Madurai for his guidance and encouragement in preparing this dissertation.

My heartfelt thanks to **Dr.I.Chandrasekaran** M.D., D.A., Additional Professor of Anaesthesiology, Madurai Medical College, Madurai for his guidance in doing this work.

My sincere thanks to **Dr.S.P.Meenakshisundaram** M.D., D.A., Additional Professor of Anaesthesiology, Madurai Medical College, Madurai for his able assistance in completing this study.

I also thank my Assistant Professors and my postgraduate colleagues, Department of Anaesthesiology, Department of Obstetrics and Gynaecology and Department of General Surgery for their kind co-operation in doing this study.

My profound thanks to **Dr.Saraswathy** M.S., Dean ,Madurai Medical College and Government Rajaji Hospital, Madurai for permitting to utilize the clinical materials of this hospital in the completion of my dissertation.

Last, but not the least, I gratefully acknowledge the patients who gave their consent and cooperation for the study.

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INTRODUCTION

"For all the happiness that mankind can

gain it is not in pleasure but in relief from pain"

-JOHN DYRDEN

Pain is a fundamental biological phenomenon. The International Association for the study of pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is always underestimated and under treated. The relief of pain during surgery is the main part of anaesthesia.

The most important duty of an anesthesiologist lies in providing relief from pain throughout the intra operative period. Extending the pain relief into the post operative period is necessary for both physiological and psychological well being of the patient.

The spinal cord has taken the centre stage in analgesia practice following the demonstration of analgesia with intrathecal morphine by Yaksh and Rudy (1977). Deposition of drugs in the subarachnoid space and epidural space paved a new era for pain relief.

Present study is for comparing the efficacy of midazolam and fentanyl when administered intrathecally in association with bupivacaine.

AIM OF STUDY

To evaluate and compare the efficacy of intrathecally administered midazolam and fentanyl in combination with hyperbaric bupivacaine with respect to the time of onset, duration of sensory block, quality of intraoperative anaesthesia, duration of effective postoperative analgesia and incidence of side effects.

REVIEW OF LITERATURE

1. Mac Donald R.L. and Young A.B in 1981 demonstrated GABA mediated inhibition of the spinal cord neurons in vivo and in primary dissociated cell culture.
2. In 1990 Wal dovel H.J and coworkers conducted a study on the regional cellular and subcellular distribution of GABA and benzodiazepine receptors. The highest density of GABA receptors and benzodiazepine receptors are localized as a dense band within lamina II of the dorsal horn with moderately high concentration in lamina I and III.
3. Nishiyama et al in 1992 used epidural midazolam in varying doses along with bupivacaine for pain relief in 47 patients who underwent upper abdominal surgery and it was concluded that the optimal dose of midazolam in epidural for postoperative analgesia without producing significant sedation was 0.05 mg/Kg.
4. Serrao J.M and coworkers in 1992 did a comparative study on the effects of intrathecal midazolam and intrathecal steroids for the treatment of chronic mechanical low backache. Both treatments caused a significant pain relief in 50-75% of patients. But the use of self administered analgesics was less with midazolam group than the steroid group.
5. In 1994 Australian Society for Clinical Experimental Pharmacologists and Toxicologists conducted a study on the GABA receptors and demonstrated the presence of non A non B GABA receptors. These were known as Novel receptors.
6. In 1996 Valentine J.M and coworkers compared the postoperative analgesia provided by intrathecal bupivacaine, intrathecal bupivacaine and morphine, intrathecal bupivacaine and midazolam and intrathecal bupivacaine and morphine and midazolam in patients undergoing caesarean sections. The use of patient controlled analgesia was greater with plain bupivacaine group and patients given intrathecal morphine had pruritus. The intrathecal midazolam provided useful analgesia without side effects.

7. Clinical Journal for Pain, 1996 March, states that epidural and intrathecal midazolam is more effective against somatic pain.
8. In 1998 Nishiyama and coworkers observed the in vitro changes in the transparency and pH of CSF caused by adding midazolam and bupivacaine to saline. CSF pH and transparency were not altered by adding 5mg of midazolam in10ml of saline.
9. A study was conducted in Department of Anesthesiology and Intensive care, All India Institute of Medical Sciences, New Delhi, India by Bharti N, Madan R, Mohanty P.R, Kaul H.L which was published in Acta Anaesthesio Sand. 2003, about the antinociceptive action of intrathecal midazolam.

    They randomly selected two groups and gave 15mg of bupivacaine in one group and 15mg of bupivacaine and 1mg of midazolam for another group. They concluded that addition of intrathecal midazolam to bupivacaine significantly improved the duration and quality of spinal anaesthesia and provided prolonged postoperative analgesia without significant side effects.
10. A study was conducted in Department of Anesthesiology, Samsung Medical Centre, Korea by M.H.Kim and Y.M.Lee which was published in British Journal of Anesthesia 2001, about the potentiation of analgesic effect of intrathecal bupivacaine by intrathecal midazolam.

    These groups of patients were randomly allocated and control group received 5mg of bupivacaine and 0.2ml of 0.9%saline, second group received 5mg of bupivacaine and 1mg of midazolam and third group received 5mg of bupivacaine and 2mg of midazolam. They concluded that time to first analgesia was significantly greater in the midazolam groups than in the placebo and significantly less in the patients with the second group than in the third.
11. A comparative study of intrathecal midazolam and bupivacaine with midazolam for postop analgesia was conducted in Mahatma Gandhi Institute of Medical Sciences by Dr.Ravikumar, Dr.Domkendur and Dr.S.Dhawade.

    They randomly allocated two groups, Group M and Group B each with 50 patients. Group B

received 20mg of bupivacaine and Group M received 10mg of bupivacaine and 1mg of midazolam intrathecally. They concluded that addition of midazolam to bupivacaine intrathecally provided better postoperative analgesia without any adverse effect.

12. A study about effect of midazolam with intrathecal bupivacaine for vaginal hysterectomy was conducted by Neeraj Bharti, R.Madan, R.P.Mahanty at All India Institute of Medical Sciences, New Delhi.

    They selected 60 ASA I and II female patients undergoing vaginal hysterectomy and randomly allocated them into 3 groups. Group A received 3ml of 0.5% bupivacaine, Group B received 2.5ml of 0.5% bupivacaine with 1mg of midazolam in 0.5ml of normal saline and Group C received 2ml of bupivacaine with 2mg of midazolam in 0.5ml of normal saline. They observed duration of sensory, motor, perioperative analgesia along with hemodynamic variability and sedation. They concluded that intrathecal midazolam can be used as bupivacaine sparing drug especially in elderly and high risk patients to reduce the hemodynamic variability and to increase postoperative analgesia.

13. A study of comparative evaluation of intrathecal bupivacaine and intrathecal bupivacaine midazolam combination on postoperative analgesia was done at Maulana Azad Medical College and Lok Nayak Hospital, New Delhi by Dr.Nitesh Agarwal and Dr.Bhadma. They randomly divided the patients into two groups, 25 patients in each group. Group B received 3ml [15mg] of 0.5% bupivacaine with 0.2ml of normal saline and Group BM received 3ml [15ml] of 0.5% bupivacaine and 0.2ml [1mg] of midazolam. They concluded that combination of intrathecal midazolam and bupivacaine provides longer duration of postoperative analgesia as compared to intrathecal bupivacaine alone.

14. Works of Matan in 1900 combining morphine with intrathecal cocaine appears to be one among the first attempt to enhance spinal anaesthesia with spinal opioids.

    In 1901 two independent reports, one by a Japanese anaesthesiologist and the second by a

Romanian Surgeon, had been published as opioids for intrathecal anaesthesia.

In 1965 Gate control theory of pain proposed by Melzack and Wall focused on the importance of dorsal horn of spinal cord in the modulation of pain.

In 1973 Pert and Snyder identified specific opiate receptors in the substantia gelatinosa of dorsal horn of spinal cord.

In 1976 Yaksh and Reddy suggested that intrathecal opioids act at the presynaptic receptors in the substantia gelatinosa and block the release of neurotransmitters.

This study was undertaken in rats.

In 1980 Danir et al identified that respiratory depression due to intrathecal morphine was reversed by naloxone without reversing analgesia.

In 1984 Huand H.J, Ishimain T, Yambe studied the use of intrathecal morphine for postoperative pain relief.

15. A study of effect of intrathecal fentanyl added to hyperbaric bupivacaine for caesarean section was conducted at Department of Anaesthesiology, Tokyo University School of Medicine, Tokyo.24 patients posted for elective caesarean section were allotted to receive either 15mcg of fentanyl or 0.9% normal saline added to 2ml of 0.5% hyperbaric bupivacaine intrathecally in right lateral decubitus position. They concluded that addition of fentanyl to intrathecal bupivacaine in parturient undergoing caesarean section improved quality of anesthesia without producing side effects.
16. A study conducted by Dr.Biswas, Dr.Nath, Dr.Bhattacharjee was published in Indian Journal of Anaesthesia 2002 about intrathecal fentanyl added to hyperbaric bupivacaine improving analgesia during caesarean section and early postoperative period.

They randomly allotted 40 parturients coming for elective caesarean section into two groups. Group 1 received 2ml of 0.5%bupivacaine with 0.25ml of 0.9%saline.Group 2 received 2ml of 0.5%bupivacaine with 0.25ml (12.5mcg) of fentanyl.They concluded that 12.5mcg of fentanyl added to intrathecal bupivacaine could markedly improve intraoperative anaesthesia and significantly reduce the

demand for postoperative analgesia with good maternal satisfaction and fetal well being.

17. A comparative study of intrathecal hyperbaric bupivacaine with fentanyl and bupivacaine alone for urological surgeries was done by Dr.Saravanan, Dr.Madankumar, Dr.Balamanimukizhan at Madras Medical College, Chennai. 80 patients posted for elective urological surgeries were allotted into 4 groups with each group containing 20 patients.

    Group A received 10mg hyperbaric bupivacaine and 0.5ml of distilled water intrathecally

    Group B received 10mg hyperbaric bupivacaine and 0.5ml (25mcg) of fentanyl

    Group C received 7.5mg of hyperbaric bupivacaine, 0.5ml of distilled water and 0.5ml (25mcg) of fentanyl

    Group D received 5mg of hyperbaric bupivacaine, 25mcg of fentanyl and 1ml of distilled water.

    They concluded that addition of 25mcg of fentanyl to 0.5%hyperbaric bupivacaine markedly prolongs the postoperative analgesia without side effect. It also facilitates the use of smaller doses of bupivacaine in subarachnoid space.

HISTORY

SUB ARACHNOID BLOCK:

The first neuraxial block was performed by James Leonard Corning, who also coined the term “Spinal anaesthesia” on October 12; 1865.He injected cocaine 120mg between T11 and T12 spinous process, and obtained loss of sensation due to epidural block rather than a subarachnoid block.

Further advances took place in Keil, Germany where August Bier and his assistant August Hilderbrant used Quinke’s method to enter the intrathecal space and injected 5-15mg of cocaine to produce spinal anaesthesia. This happened on August 16, 1898.

This was followed by successful and enthusiastic practice of spinal anaesthesia by others:

- J.B Selclowitsch of St.Petersburg on May 11, 1899
- Theodre Juffier in France on November 9, 1899 and
- Rudolph Mates in New Orleans in November 10, 1899.

Barker advised meticulous sterile technique and introduced hyperbaric solutions.

Serious complications from spinal anaesthesia were soon observed. In 1900, F.Gumprecht observed 15 cases of sudden death from lumbar puncture.

After an infamous malpractice trial in 1953 ,which saw healthy patients developing spastic paraparesis after spinal anaesthesia ,came a reassuring study of 10,098 spinal anaesthesia with only 71 minor neuropathies in 1954. This allowed spinal anaesthesia to emerge as a safe anaesthetic technique.

LOCAL ANAESTHETICS:

1855 : Friedrich Gaedicke of Germany isolated the first local anaesthetic agent cocaine.

1860 : Albert Neimann purified and named the alkaloid as cocaine.

1884 : Carl Koller an opthamalogist from Vienna demonstrated the local analgesic properties of cocaine on the cornea.
William Halstead recognized the ability of injected cocaine to interrupt nerve impulse conduction, leading to the introduction of peripheral nerve block anaesthesia and spinal anaesthesia.

1885 : J.L.Corning produced analgesia by neuraxial injection of cocaine.

1904 : Ernest Foureau synthesized stovaine.

1905 : Einhorn introduced the first synthetic local anaesthetic, procaine.

1943 : Lofgren synthesized the first amide local anaesthetic lidocaine.

1947 : Torsten Gordh made the first clinical use of lidocaine.

1957 : Ekenston et al of Sweden synthesized bupivacaine.

1963 : L.J.Tulivuo first used bupivacaine, clinically.

OPIOIDS:

1803 : Morphine was isolated from opium by Serturner.

1832 : Codeine was isolated.

1848 : Papavarine was introduced.

1939 : Meperidine was synthesized and it was used for anaesthesia with nitrous oxide.

1942 : Nalorphine a mixed agonist-antagonist was introduced.

BENZODIAZEPINES:

Benzodiazepines were discovered to be effective sedative and hypnotic drugs.

1955 : Sternbach synthesized chlordiazepoxide.

1959 : Sternbach synthesized diazepam.

1961 : Oxazepam, a metabolite of diazepam was synthesized by Bell.

1971 : Lorazepam was introduced. It was the first clinically used water soluble benzodiazepines.

1977 : Specific receptor for benzodiazepines was identified.

Midazolam was the first benzodiazepine that was produced primarily for use in anaesthesia.

ANATOMY OF SUBARACHNOID SPACE

Subarachnoid local anaesthetics effect their sensory block at the spinal cord, which is continuous cephalad with the brain stem via foramen magnum and terminates distally in the conus medullaris. The distal termination, because of differential growth rates between bony vertebral canal and central nervous system, varies from L_3 in the infant to L_1 in the adult.

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to periphery): the piamater, subarachnoid mater and duramater. The piamater is a highly vascularised membrane that closely invests the spinal cord. The arachnoid mater is a delicate non vascular membrane closely attached to the outermost layer, the duramater. Between these two innermost layers

is the space called as subarachnoid space. In this space are the CSF, spinal nerves, a trabecular network between two membranes, blood vessels that supply the spinal cord and the lateral extensions of the piamater and the dentate ligaments, which provide lateral support from the cord to the duramater.

Although the spinal cord ends at $L_{1,}$ the subarachnoid space continues to $S_{2.}$ The third and the outermost layer in the spinal cord is the longitudinally organized fibroelastic membrane, the duramater. This layer is the direct extension of the cranial dura and extends as spinal dura from the foramen magnum to $S_{2,}$ where the filum terminale blends with the coccyx.

PAIN – PHYSIOLOGICAL CONSIDERATION

Pain which may serve a number of useful defensive functions, when associated with actual or potential tissue damage, can be an unpleasant sensory and emotional experience. Relieving pain is one of the most tangible roles the anaesthesiologist can play.

There are two major theories of pain:

1. Specificity theory proposed by Vonfrey states that pain is due to stimulation of specific end organs.
2. Intensive / Summation pattern theory proposed by Scheides states that there are no specific pain receptors and any sensory stimulus if sufficiently severe would produce pain.

NEUROANATOMY:

Painful stimuli which can be mechanical, thermal, electrical or chemical activate specific nociceptors in the tissues. Nociceptive receptors are fine, profusely branched free nerve endings

covered by Schwann cells with little or no myelin.

Receptors are of two types.

One group responds to mechanical deformation and are described as high threshold mechanoceptors and others respond to a variety of noxious inputs and are polymodal nociceptors. These receptors responds to mechanical, thermal and chemical stimuli like H^+,K^+,histamine, serotonin, bradykinin, prostaglandin and substance P.

Fibre type	**Aδ finely myelinated**	**'C'unmyelinated**
Diameter	2 – 5 μm	0.3 – 1.3 μm
Conduction velocity	5 -15 ms^{-1}	0.5 – 2 ms^{-1}
Distribution	Body surface, muscles and joints.	most tissues.
Character of pain	Sharp and pricking pain	Delayed Diffuse dull aching.
Effect	Felt quickly, well localized withdrawal reflex.	Threshold for response is higher.

PRIMARY AFFERENT CONDUCTION:

The cell body of these nerve endings lies in the dorsal root ganglia. Central terminations of these fibres are in the dorsal horn of the spinal cord. Majority of the fibres enter into the spinal cord dorsal horn in the ventrolateral bundle. On entering the cord the roots divide into ascending and descending branches which may enter the dorsal horn one or two segments above or below the segment of origin.

DORSAL HORN OF THE SPINAL CORD:

Dorsal horn of the cord is divided into laminae on the basis of their histological appearance. There are numerous connections between the laminae although they do have discrete functions related to pain processing. Laminae II, the substance gelatinosa, extends from the terminal nucleus in the medulla to the filum terminale, C fibres terminate in lamina II. Aδ fibres terminate in lamina I and lamina V. Aβ fibres terminate in lamina I and lamina V. Aβ fibres which respond to innocuous stimuli such a vibration and light touch enter the cord medial to the dorsal horn and pass without synapse to the dorsal column. They give off collateral branches to the dorsal horn which terminate in laminae particularly III and IV and deeper. They also synapse directly with terminals of unmyelinated C fibres in lamina II. The laminae that receive afferent input from both large and small diameter fibres are important sites for pain modulation and localization. From lamina III and deeper, information is summated from direct input from the periphery and from dorsal laminae.

The extent to which painful peripheral stimuli are conducted centrally and perceived as pain depends upon the degree to which two major modulating mechanisms at the level of dorsal horn close

the gate to onward transmission.

The Gate Control Theory proposed by Melzack and Walls:-

1. Activity of large myelinated Aβ fibres is via inhibitory circuits in the superficial laminae of the dorsal horn to suppress the transmission in small unmyelinated 'C' afferents.
2. Inhibitory control from higher centres is tonically active. From the dorsal horn, nociceptor neurons ascend in the contralateral spinothalamic and spinoreticular tracts in the anterolateral white matter of the cord.

The spinothalmic tract principally comprises of axons of neurons in lamina I and V of the dorsal horn, in which most of the Aδ fibres terminate. These ascend to the central posterior lateral nucleus of the thalamus and thence to the post central gyrus. Axons are somato topically organized, with caudal elements found laterally and those from the rostral structures arranged centrally, in the nerve. The spinothalmic tract sends collateral branches to the periaqueductal grey matter in the mid brain.

The spinoreticular pathway arises from cells deeper in the grey matter of the dorsal horn including lamina V. Fibres ascend in the anterolateral cord and reach the nuclei of the brain stem reticular formation, whence they project to the thalamus, hypothalamus and thalamic inter laminar nucleus. The later project diffusely to the whole of the cerebral cortex. This system shows little somatotopic organisation and is involved in the perception of diffuse emotionally disturbing pain.

DESCENDING INHIBITORY PATHWAYS:

These cause modulation of pain perception. Electrical stimulation of periaqueductal grey

produce profound analgesia, but responses to non noxious stimuli remains normal and subjects are alert. Injection of morphine in this region produces greater analgesic effect. Periaqueductal grey receives input from thalamus, hypothalamus, cerebral cortex and collaterals from spinothalmic tract. So, it is an important centre for descending control of pain. It projects into nucleus raphe magnum in the medulla. Axons from the nucleus descend in the dorsolateral funiculus of the spinal cord to the dorsal horn.

OTHER INHIBITORY PATHWAYS:

1. **Large primary afferent fibres:**

   A§ fibres with cell bodies in the dorsal root ganglia send their central projections ascending in the dorsal column. They send collaterals to synapse with and activate inhibitory inter neurons which inhibit release of transmitter along pain pathways.

2. **Endogenous opiates:**

   Encephalin, bendesphir and dynorphins, are derived from biologically inactive peptide precursors produced in cell body of neurons and transported to axon terminal. Distributed widely in central nervous system, but particularly in sites associated with pain. They act as endogenous ligands for opioid receptors producing primary inhibitory effects.

3. **Amines:**

   Noradrenaline is involved in descending modulation of pain, probably acting via α_2 receptor. Serotonin is also involved in descending modulation of pain. All serotonin receptor

subtypes are probably involved.

4. **GABA:**

Evidence strongly suggests that GABA mediates the inhibitory action of local interneurons in the brain and it mediates presynaptic inhibition within the spinal cord.

FUNCTIONS OF PAIN CENTRES:

Thalamus- experience of pain is the main function. The post central gyrus is for accurate localization of pain. The prefrontal cortex produces affective unpleasant reaction to pain. Fast and slow conductance explains the double sensation of pain following brief painful stimulus. More distal the stimulus more distinct can two successive peak be felt.

MEDIATORS OF PAIN:

Peripheral mediators are prostaglandin E & I, autocoids such as bradykinin, acetylcholine, histamine, 5 hydroxytryptamine, leukotrienes and cytokines.

Brain and spinal cord mediators are substance P-the principle transmitter, hydrogen ions, vasoactive intestinal polypeptide glutamate and aspartate.These mediators cause distortion of the terminal region of neurons, modifying the ion permeability and interfering with propagation of impulses.

ADJUVANTS TO LOCAL ANAESTHETICS IN SPINAL ANAESTHESIA

Local anesthetic agents have been widely used in spinal anaesthesia.One of the main disadvantage is the limited duration of block achieved with local anaesthetics.To overcome this, various adjuvants have been tried and used successfully. This addition of adjuvant has further expanded the advantage of regional anaesthesia over general anaesthesia.

ADJUVANTS:

These may be opioids like morphine, fentanyl, sufentanil or buprenorphine. It may be benzodiazepines alpha 2 agonist clonidine, acetylcholine esterase inhibitors like neostigmine, NMDA receptor antagonist ketamine or nonsteroidal anti inflammatory agents.

These adjuvants usually confer the advantages of

- Rapid onset time
- Differential blockade
- Inhibition of tourniquet pain
- Improved and prolonged duration of post operative analgesia.

Also these adjuvants decrease the amount of local anesthetic required to produce same effect thereby reducing the risk of local anesthetic toxicity, hypotension and profound motor blockade.

OPIOIDS

The term opioids refer to all compounds related to opium, derived from juice of opium poppy, papaver somniferum. Opiates are the term used for drugs derived from opium. Morphine is the prototype opioid. Opioid compounds can be classified as naturally occurring, semisynthetic and synthetic opioids. With the development of synthetic drugs with morphine like effects, the term opioid is now used to refer to all exogenous substances, natural and synthetic that binds to opioid receptors and produces some agonistic effects.

CLASSIFICATION:

Naturally occurring opioids are divided into two chemical classes

1. Phenanthrenes-eg. Morphine and codeine
2. Benzylisoquinolones-eg. Papavarine

Semisynthetic opioids result from relatively simple modification of morphine molecule.eg.diacetylmorphine.

Synthetic opioids contain phenanthrene nucleus. They are classified into four subdivisions.

1. Morphinan derivatives-eg.levorphanol
2. Methadone derivatives-eg.methadone
3. Benzomorphan derivatives-eg.pentazocine
4. Phenylpiperidine derivatives-eg.meperidine, fentanyl, sufentanil, alfentanil

OPIOID RECEPTORS:

The presence of opioid binding sites in the nervous system was reported in the year 1973. Immuno histochemical studies have demonstrated opioid receptors in various areas of the central nervous system. These indude the amygdala, the mesencephalic reticular formation, the periaquiductal gray matter and the rostral ventral medulla.

Based on pharmacological experiments three types of opioid receptors were published.

(i) mu or μ for morphine type

(ii) Kappa or K for Ketocyclazocinetype

(iii) Sigma or σ for SKF 10047 type

In addition two other receptors have been indentified in the vas deferens of mouse namely the delta (σ) and epsilon (∑) receptors. All the receptors bind to a super family guanidine protein coupled receptors.

The mu or morphine preferring receptors are principally responsible for supra spinal and spinal analgesia. Various subtypes have been proposed based on post translational modification of μ receptor. μ_1 rceptor is speculated to produce analgesia, while μ_2 receptor is responsible for hypotension, bradycardia and respiratory depression. Delta receptors serve to modulate the activity of μ receptor. Kappa receptors are those to which most of the opioid agoinst – antagonist bind. Respiratory depression is less common with Kappa receptor activation than μ. Dysphoria and diuresis may occur. High intensity painful stimulations are resistant to the analgesic effect of Kappa receptor activation.

CHARACTERISTIC OF OPIOID RECEPTORS

		Mu (μ_1)	**Delta (σ)**	**Kappa (K)**
1	Endogenous Ligand	β-endorphin endomorphine	Leu-enkephalin Metenkephalin	Dynorphin
2	Agonist	Morphine Fentanyl	DPDPE Deltorphin	Buprenorphine Pentazocine
3	Antagonist	Naloxone Naltrexone	Naloxone Naltrindole	Naloxone Nor BNI
4	Coupled G Protein	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
5	Adenylate cyclase	Inhibition	Inhibition	Inhibition
6	Effect	Analgesia Supraspinal and spinal (μ_1) Euphoria (μ_1) Respiratory Depression (μ_2) Bradycarrdia (μ_2) Constipation (μ_2)	Analgesia Respiratory Depression Constipation (minimal)	Analgesia (Spinal) Dysphoria Sedation Miosis Diuresis.

PHARMACOLOGICAL ACTIONS OF OPIOIDS

		Receptor	Action	
			Agonists	**Antagonists**
1	Supraspinal Spinal	μ, σ, k μ, σ, k	Analgesic Analgesic	No effect No effect
2.	Respiratory function	μ	Decrease	No effect
3.	Gastro intestinal tract	μ, k	Decrease transit	No effect
4.	Psychotomimesis	k	Increase	No effect
5.	Feeding	μ, σ, k	Increase	Decrease
6.	Sedation	μ, k	Increase	No effect
7.	Diuresis	k	Increase	-
8.	Harmone secretion (a)Prolactin (b) growth hormone	μ μ and σ	Increase release Increase release	Decrease release Decrease Release

MECHANISM OF ANALGESIC ACTION:

Opioids act as agonists at stereospecific opioid receptors at presynaptic and post synaptic sites in the central nervous system and also outside central nervous system in peripheral tissues.

MECHANISM OF ACTION IN CENTRAL NERVOUS SYSTEM:

The analgesic effect of opioids results from their ability to directly inhibit the ascending transmission of nociceptive information from the spiral cord dorsal horn. It has a descending inhibitory analgesic action by activation of pain control circuits that descend from the midbrain via the rostral ventromedial medulla (RVM) to the spinal cord dorsal horn. In addition, local spinal mechanisms also take part in the analgesic action of opioids.

Existence of the opioids in the ionized state is necessary for strong binding at the anionic opioid receptor site. Stereochemically, levorotatory forms are found to be most active. The affinity of most opiod agonists for receptors correlated with their analgesic property.

The principal effect of opioid receptor activation is a decrease in neuro transmission. This decrease in neuro transmission is largely due to presynaptic inhibition of neurotransmitter release, although post synaptic inhibition of evoked activity may also occur. The neurotransmitters whose release are also inhibited include acetylcholine, dopamine, norepinephrine and substance P.

The intracellular biochemical events activated by binding of opioid agoinst to opioid receptor are

(i) increased potassium conductance – leading to hyperpolarization

(ii) Calcium channel inactivation

Both of which produce an immediate decrease in neurotransmitter release.

Opioid receptors mediated inhibition of adenylate cyclase, causing a decrease in cellular cAMP has delayed effect, via a reduction in cAMP responsive neuropeptide genes and a reduction in

neuropeptide mRNA concentrations.

MECHANISM OF ACTION IN PERIPHERAL TISSUES:

Opioids are effective in inflammatory hyperalgesic conditions. The opioids bind to receptors in the primary afferent neurons and mimic the action of endogenous ligands, resulting in the activation of pain modulating (antinociceptive) systems.

EFFECT OF OPIOIDS ON VARIOUS SYSTEMS OF THE BODY:

These can be classified into therapeutic drug effects and non-therapeutic drug effects.

THERAPEUTIC DRUG EFFECTS:

OPIOIDS AS ANAESTHETICS:

The capacity of opioids to produce anesthesia is debated. General anaesthesia can be considered in terms of its component parts; amnesia, analgesia, unconsciousness, immobility, muscle relaxation and control of autonomic and endocrine responses to surgery.

Of these, opioids produce effects of analgesia, unconsciousness and control of autonormic and endocrine responses to surgery. Butorphanol has been reported to produce anterograde amnesic effect.
Shivering: Post anaesthetic shivering, that is unrelated to hypothermia can be effectively abolished by certain opioids like meperidine, butorphanol and tramadol.

CENTRAL NERVOUS SYSTEM:

Opioids generally produce modest decrease in cerebral methabolic rate (CMR). They cause decrease in cerebral blood flow when co administered with nitrous oxide and a cerebral vasodilating anaesthetics. Opioids affect intracranial pressure minimally, but may cause increase in intracranial pressure when compliance is compromised.

NON THERAPEUTIC DRUG EFFECTS:

While opiods have proved to be relatively safe drugs,management of side effects is critical to successful application in clinical practice.

RESPIRATORY EFFECTS:

Opioids decrease resting minute ventilation and tidal volume. Respiratory rate may be decreased or normal, whereas μ agoinsts produce a dose related depression of breathing. Ventilatory responses to hypoxia and hypercarbia are blunted. Sufficient doses may produce, apnoea, but the apnoeic conscious patient may breathe on command.

CARDIOVASCULAR EFFECTS:

The action of opioids on cardiovascular system is mostly due to histamine release. Morphine or meperidine which cause release of histamine provide hypotension and tachycardia.

Opioids also depress contractility of isolated heart muscle, but at doses greatly in excess of those used clinically. An exception to this is meperidine which produce myocardial depression at clinically relevant concentrations. Morphine and fentanyl analogs decrease heart rate due to vagominetic action. On the otherhand, meperidine, due to its anticholinergic properties increase heart rate.

RIGIDITY:

Opioid induced muscle rigidity occurs usally during induction of anaesthesia, especially with largers doses. This rigidity is central in origin, being mediated by μ receptors in brainstem medulla.

NEUROEXCITATORY EFFECTS:

Opioids are also associated with tonic – clonic movements or myoclonus.

GASTRO INTESTINAL EFFECTS:

These effects manifest by a combination of central and peripheral actions. The effects observed are decrease in intestinal motility and increase in the tone of sphincter of Oddi. Nausea and vomiting is a commonly observed effect of opioids due to its stimulation of receptors at chemoreceptor trigger zone.

PRURITIS:

It is a common opioid-induced side effect, especially with neuraxial opioids.

INTRATHECAL OPIOIDS

In the context of "Augmentation strategies" for spinal anaesthesia, the discovery of opioid receptors and the development of technique of intrathecal opioid administration is one of the most significant advances in pain management in the last three decades. Plethora of studies have shown that spinal opioids can provide profound post operative analgesia with fewer neurological and systemic side effects than with systemic opioids. This is because neuraxial opioids, in contrast to local anaesthetics, do not cause sympathetic block, skeletal muscle weakness or lack of proprioception.

BRIEF HISTORY:

In 1900, Matas discovered that the adverse effects of intrathecally administered cocaine could be mitigated with the addition of morphine. He used 1.5mg morphine intrathecally to reduce the central nervous system effects of cocaine.

In 1901, a Japanese anesthesiologist Otojiro Kitagawa, used 10mg of morphine with local anaesthetic eucaine intrathecally for cancer pain relief.

With the discovery of opioid receptors in the spinal cord, intrathecal opioid administration quickly spread to perioperative care in a wide array of surgical procedures.

PHARMACODYNAMICS:

The exact mechanism of local anaesthetic – opioid interaction remains unkown, despite detailed characterization of opioid receptor system at the cellular and molecular level.

When administered alone, spinal opioids selectively modulate C and A fibres with minimal impact on dorsal root axons. Somatosensory evoked potentials remain intact with respect to nerve conduction block. None of the opioids exhibit local anaesthetic property except possibly meperidine.

Local anaesthetics potentiate the antinociceptive effect of morphine, without an enhancement in motor block. Transient change in temperature perception has been observed with spinal meperidine, fentanyl and sufentanil.

The dorsal root entry zone is speculated to be the active site for conduction block for spinal opioids. The hormonal milieu (pregnancy) also contributes to drug effectiveness. Spinal progesterone has been found to potentiate the analgesic effects of spinal sufentanil in rats.

PHARMACO KINETICS:

It is believed that hydrophilic opioids remain unbound in the CSF for a long time and hence to move rostrally in the CSF, thereby resulting in delayed respiratory depression. (eg) morphine.

In contrast lipophilic opioids do not move rostrally in CSF, but move more rapidly than hydrophilic opioids from CSF to spinal cord. But recently,studies have shown that even lipophilic opioids do not remain localized near their site of injection and they may rapidly move from lumbar intrathecal injection sites to cervical and brain stem levels via CSF.

ONSET OF ACTION:

Lipophilic opioids spread more rapidly from the CSF into the spinal cord. Hence they have faster onset of action (eg.fentanyl) than hydrophilic opioids. The delayed onset of action of morphine, a hydrophilic opioid may in fact limits its utility as an intra operative adjuant.

ANALGESIC MECHANISMS:

The effect of intrathecally administered opioids are determined by the pharmacodynamics and pharmacokinetics of each individual drug. The dorsal horn of the spinal cord is richly populated with opioid receptors. Majority of these are localized within substansia gelatinosa. Upon receptor activation, a G protein mediated effects result in inhibition of adenyl cyclase and inward flux of potassium. This flux results in membrane hyperpolarization and decrease in neural excitability (anti nociceptive effect). Opioids may act at synapses in spinal cord either presynaptically or postsynaptically.

μ receptor activation results in the presynaptic inhibition of substance P release, a compound that would otherwise result in the activation of an integrated pain signal.

All clinically useful intrathecal opioids are strong μ receptor agoinsts within the dorsal horn. Their supra spinal and spinal effects act synergistically to blunt somatic as well as visceral pain. But analgesic effect is more specific for visceral pain. Analgesia of neuraxial opioids is also dose related.

DURATION OF ACTION:

The duration of analgesic action will depend upon the efficacy, lipophilicity, receptor affinity

and the dose of the drug administered. Less lipid soluble drugs (eg morphine) will remain in the CSF for a longer time and hence will produce longer duration of analgesia than a highly lipophilic opioid like fentanyl.

High lipophilicity favours more rapid removal of the drugs from the receptor site into the blood stream, which limits the duration of action, only exception to this being buprenorphine.

POTENCY:

H.J.MCQuay et al in 1989 published that the intrathecal potency is defined as the amount of drug required to produce a particular degree of receptor occupancy .It is inversely related to their lipid solubility and related directly to the affinity of the drug for the receptor. The inverse correlation between intrathecal potency and lipophilicity may be due to the nonspecific binding of highly lipophilic agents to the lipid rich fibres capping the dorsal horn, limiting their access to the opioid receptors. Highly soluble opioid pethidine, is least potent and has to be used in systemic doses for intrathecal administration.

SIDE EFFECTS:

Opioids injected into the lumbar CSF may spread passively cephalad by diffussion and concentration gradient effect, aided by arterial pulsation and respiratory movements over a time course of 6 – 8 hours. They may reach the vicinity of the cisterna magnum and brain tissue of fourth ventricle. This explains the occurence of nausea, vomiting and respiratory depression after intrathecal administration.

Incidence of side effects is dose related and larger doses are clearly associated with higher incidence of side effects.

NAUSEA AND VOMITING:

Opioids commonly produce nausea and vomiting.The vomiting center in medulla receives inputs from many centers including the chemoreceptor trigger zone, which contain opioid receptors among others, that promote vomiting. But it has been observed by Dahlgren et al that spinal opioids administred along with local anaesthetics in spinal anaesthesia for cesarean sections decreased the requirement of intraoperative antiemetic medication.

Cooper et al reported a significant reduction in intraoperative nausea with an addition of spinal fentanyl to a spinal anaesthetic for cesaerean delivery. The effects are due to the dense sensory blockade achieved by the addition of opioids to local anaesthetics in spinal anaesthesia.

PRURITIS:

It is a peculiar and the most common side effect with neuraxial opioids. It is not confined to the segmental area of analgesia, but may be generalized or localized to the face, neck or upper thorax. Pruritis is usually very mild, severe pruritis occurring in about 1% of patients. Pruritis is more likely to occur in obstetric patients, perhaps due to interaction of estrogen with opioid receptors.

Though opioids may release histamine from mast cells, this is not the mechanism for pruritis.Pruritis may be due to a generalized modulation of cutaneous sensation or in the case of neuraxial opioids, due to cephalad migration of the opioid in the CSF and subsequent interaction with

opioid receptors in the trigeminal nucleus. Pruritis may or may not be dose related.

URINARY RETENTION:

This is usually encountered with hydrophilic spinal opioids. Urinary retention occurs most likely due to the interaction of opioids with opioid receptors in sacral spinal cord. This promotes inhibition of sacral parasympathetic nervous system outflow causing detrusor muscle relaxation and an increase in maximal bladder capacity. There is also an increase in vesical sphincter tone. All these factors results in urinary retention. This effect is usually not dose related.

RESPIRATORY DEPRESSION:

This is a major problem, limiting the use of spinal opioids. Respiratory depression may occur early or late. Early respiratory depression is usally mild, occur due to vascular uptake of drugs and occurs within one hour with morphine and within minutes with lipophilic opioids.

Late respiratory depression more problematic and occurs 4 – 18 hours following intrathecal administration. This is due to the cephalad spread of drug in the CSF. Highly lipophilic opioids dissolve readily in neural tissue (segmental localization), thus limiting the drug available for cephalad spread. Hence, lipophilic opioids are considered safe with regard to late onset respiratory depression.

Factors which predispose to development of respiratory depression after intrathecal opioids are advanced age, high risk patients, larger dose of opioids, use of hydrophilic opioids, intrathecal administration as compared with epidural, concominant use of parenteral opioids or sedatives or both, opioid sensitive patients and thoracic epidural administration.

Obstetric patients are at lesser risk for ventilatory depression, perhaps because of the increased stimulation of ventilation by progesterone.

SEDATION:

This effect is dose related and occurs with all opioids. Whenever sedation occurs, depression of ventilation should also be considered.

CENTRAL NERVOUS SYSTEM EXCITATION:

Tonic skeletal muscle rigidity resembling seizure activity is a well known side effect of intravenous opioids, but is rarely observed with neuraxial opioids. Myoclonic activity has been observed after neuraxial opioids. A possible explanation for this effect is the cephalad migration of the opioid in CSF and subsequent interaction with non opioid receptors in the brain stem or basal ganglia. In this regard, opioids may block, glycine and gamma amino butric acid mediated inhibition.

ANTAGONISM:

Systemically administered naloxone can antagonize all the side effects of spinal opioids including respiratory depression. Repeated doses may be required to maintain adequate ventilation. Prophylactic administration of naloxone has also been recommended by some to prevent pruritus, nausea, vomiting and other side effects. Analgesic effect is usally affected by naloxone.

MERITS AND DEMERITS OF SPINAL OPIOIDS:

MERITS:

- Greater success rate of spinal anaesthesia
- Faster onset of surgical block than local anaesthetic alone
- Improved intra operative analgesia (enhanced sensory block without increased motor block)
- Reduction in the dose of local anaesthetics with faster recovery from spinal anaesthesia
- Post operative analgesia beyond duration of local anaesthetic block

- Less nausea and vomiting

DEMERITS:

- Frequent pruritus
- Sedation (never with lipophilic opioids)
- Rare respiratory depression (especially late onset)
- Rare uninary retention (more with morphine)
- Nausea,vomiting, somnolence and early respiratory depression due to vascular uptake of opioids. These are dose related.

PHARMACOLOGY OF FENTANYL

Fentanyl is a phenyl piperidine derivative, synthetic opioid agonist that is structurally related to meperidine. As an analgesic fentanyl is 75 to 125 times more potent than morphine.

PHARMACODYNAMICS:

A single dose of fentanyl administed intravenously has a more rapid onset and shorter duration of action than morphine. The effect- site equilibration time is 6.4 minutes. Rapid onset is due to its high lipophilicity and shorter duration of action is due to its rapid redistribution to inactive sites such as fat and skeletal muscles. It is estimated that 75% of initial fentanyl dose is undergoing first-pass pulmonary uptake. When funtanyl is administered in continuous infusion, progressive saturation of these inactive tissue sites occur. As a resalt, the plasma concentration of fentanyl does not decrease rapidly. So the duration of analgesia, as well as depression of ventilation, may be prolonged.

PHARMACOKINETICS:

Fentanyl is extensively metabolized by N – demethylation, producing nor fentanyl, which is structurally similar to normeperidine. Nor fentanyl is excreted by the kidneys and can be detected in the urine for 72 hours after a single intravenous dose of fentanyl. Even though fentanyl has a short duration of action, its elimination half life is longer than that for morphine. This in infact due to a larger volume of distribution of fentanyl. The larger volume of distribution is due to its greater lipid solubility and then more rapid passage of drug into tissues compared with less lipophilic morphine. The plasma concentrations of fentanyl are maintained by slow reuptake from inactive tissue sites, which account for its persistent effect.

CONTEXT SENSITIVE HALF TIME:

As the duration of continuous infusion of fentanyl increases beyond about 2 hours, the context sensitive half-time of this opioid becomes greater than sufentanil. This reflects the saturation of inactive tissue sites with fentanyl during prolonged infusions and return of the opioid from peripheral compartments to the plasma. This tissue reservoir of fentanyl replaces the fentanyl eliminated by hepatic metabolism so as to slow the rate of decrease in the plasma concentration of fentanyl when the infusion is stopped.

DURING CARDIO PULMONARY BYPASS:

All opioids show a decrease in plasma concentration with the initiation of cardio pulmonary bypass. The degree of this decrease is greater with fentanyl because a significant proportion of the drug adheres to the surface of the cardiopulmonary bypass circuit. Sufentanil and alfentanil may provide a stable plasma concentration during cardio pulmonary bypass. Elimination of fentanyl and alfentanil are prolonged by cardio pulmonary bypass.

CLINICAL USES:

Low dose of fentanyl, 1- 2mcg / kg, is injected to provide analgesia. Moderate dose of fentanyl, 2 – 20mcg/kg, is administered as an adjuvant to inhaled anaesthetics to blunt the circulatory responses to (a) direct laryngoscopic intubation (b) sudden change in the level of surgical stimulation. Timing of fentanyl administration to blunt these responses should consider the effect-site equilibration time.

Larger doses of fentanyl, 50 – 150mcg/kg have been used alone to produce surgical anaesthesia.

The advantage of larger and sole fentanyl administration are (a) lack of myocardial depressant effect, (b) absence of histamine release, (c) suppression of the stress responses to surgery. Disadvantages include (a) post operative depression of ventilation and (b) possible patient awarness.

Fentanyl may be administered as a oral transmucosal preparation in a delivery device designed to deliver 5 – 20mcg / kg of fentanyl. In children aged 2 to 8 years, the preoperative administration of transmucosal fentanyl 15-20mcg/.kg 45 minutes before the induction of anaesthesia, reliably induces preoperative sedation and facilitates induction of inhalation anaesthesia. But there is more chance of post operative nausea and vomiting in these patients.

Trensdermal fentanyl preparation delivering 75 to 100 mcg /hour result in peak plasma fentanyl concentrations for about 18 hours that tend to remain stable during the presence of the patch, followed by declining plasma concentration for several hours after removal of the delivery system, reflecting continued absorption from the cutaneous depot.

SIDE EFFECTS:

RESPIRATORY EFFECTS:

Persistent or recurrent depression of ventilation is a potential post operative problem. There are two theories for secondary peaks in plasma concentration of fentanyl. One is due to sequestration of fentanyl in acidic gastric fluid. This sequestered fentanyl could then be absorbed from the more alkaline small intestine back into the circulation to increase the plasma concentration of opioid and cause depression of ventilation to recur. Second is due to washout of opioid from the lungs as ventilation perfusion relationships are reestablished in the postoperative period.

CARDIOVASCULAR EFFECTS:

Carotid baroreceptor reflex control of heart rate is markedly depressed by fentanyl. Bradycardia is more prominent with fantanyl and may lead to occasional decreases in blood pressure and cardiac output.

CENTRAL NERVOUS SYSTEM EFFECT:

Seizure activity has been described to follow rapid intravenous administration of fentanyl, sufentanil and alfentanil. In the absence of EEG, it is difficult to distinguish opioid –induced skeletal muscle rigidity or myoclonus from seizure activity. Opioids may produce a form of myoclonus secondary to depression of inhibitory neurons that could produce a clinical picture of seizure activity in the absence of EEG changes.

Administration of fentanyl and sufentanil to head injury patients has been associated with modest increase in intracranial pressure despite maintanence of an unchanged $PaCO_2$. These increases in intracranial pressure are typically accompanied by decrease in mean arterial pressure and cerebral perfusion pressure.

DRUG INTERACTIONS:

Analgesic concentration of fentanyl greatly potentiate the effects of midazolam and decrease the dose requirements of propofol. The opioid – benzodiazepine combination displays marked synergism with respect to hypnosis and depression of ventilation.

PHARMACOLOGY OF MIDAZOLAM

Midazolam is an imidobenzodiazepine, water soluble benzodiazepine. Benzodiazepines were

introduced in early 1960s. Diazepam, the most popular drug of this group for the past 2 decades, is water insoluble, has a prolonged effect and is painful during injection. The unique chemical structure of midazolam confers a number of physiochemical properties that distinguish it from other benzodiazepines. This drug was synthesized in 1976 by Tryer and walser.

CHEMISTRY:

Benzodiazepines are so called because they consist of a benzene ring fused with a seven member diazepine ring. Various modification in the structure of the ring systems have yielded compounds with similar activities.

Midazolam with molecular weight of 362, has a fused imidazole that is different from classic benzodiazepines.The imidazole ring accounts for the basicity, stability of an aqueous solution and rapid metabolism. The ring exhibits a **pH dependent ring opening** phenomenon. The ring opens at pH less than 4 making the drug soluble in aqueous solution. Once midazolam enters the body, the pH changes to 7.4 and drug assumes closed ring structure and becomes highly lipid soluble. Midazolam is the most lipid soluble benzodiazepine.

PHARMACOKINETICS:

Midazolam is rapidly absorbed from gastro intestinal tract, but only 50% of the orally given drug enters the circulation, as substantial portion is metabolized during the first hepatic flow. Thus the oral dose is twice as high as intravenous dose.

Peak plasma concentrations are seen within an hour of ingestion. When given intramuscularly, the absorption is more predictable than diazepam. Being highly fat soluble it crosses blood brain barrier more easily than diazepam, to gain access to the receptors. It has a more rapid most of action. After intravenous administration of midazolam to healthy adults the disappearance of midazolam from the plasma proceeds in two distinct phases. The initial phase of rapid disappearance is due to principally to distribution of the drug while the final and slower phases of disappearance is attributable mainly to

biotransformation. Midazolam volume of distribution averages between 1 and 2.5 l/kg. Midazolam is tightly bound to plasma protein. After distribution equilibrium is reached elimination half-life varies from 1 to 4 hours. Midazolam is metabolized mainly by hepatic microsomal oxidative mechanism, by a process of hydroxylation. The fused imidazole ring is oxidized very rapidly to both 1 and 4 hydroxy midazolam. Both these products are conjugated to glucuronides and are excreted in the urine. The Metabolites have less than 1% activity of the parent drug.

FACTORS AFFECTING PHARMACOKINETICS:

Old age – Elimination half-life is increased and clearance is delayed.

1. Obesity – The Volume of distribution is increased.This increases the elimination half-life, but there is no change in the total metabolic clearance.
2. Renal insufficiency – As less than 1% of midazolam is cleared through the kidney, there is minimal alternation of its clearance in patients with renal insufficiency. The free fraction of midazolam in the plasma is increased due to decreased plasma binding.
3. Pregnancy – Midazolam crosses the placental barrier, but the placental transmission as judged by foetal – maternal plasma ratio in animals is less for midazolam than for diazepam.
4. Gender – males are more susceptible to midazolam than female patients.

MECHANISM AND SITE OF ACTION:

An important inhibitory neurotransmitter in the brain is gamma amino butric acid (GABA), while glycine is the major inhibitory neurotransmitter in the spinal cord and brainstem. The benzodiazepines augment GABA thus producing sedation and anticonvulsant activity, while anxiolysis and muscle relaxation appear to be due to glycine mimetic effects in the spinal cord and brainstem.

Among the benzodiazepines midazolam has the greatest affinity for the receptors, but dissociate faster from the receptor, thus accounting for the rapid onset and shorter duration of action. Given intrathecally or epidurally,midazolem produces analgesia which is GABA mediated.Muscle relaxation produced by midazolam is due to potentiation of glycine action on the anterior horn cells.

PHARMACODYNAMICS:

CENTRAL NERVOUS SYSTEM:

Midazolam has anxiolytic, hypnotic, anticonvulsant,muscle relaxant and anterograde amnestic properties. It decreases the cerebral metabolic rate and cerebral blood flow. Cerebral perfusion pressure decrease as the systemic pressure falls more than the intracranial pressure. Given in doses of 0.25mg/kg it does not alter intracranial tension and therefore it can be used for neurosurgical procedures. Emergence from induction is more rapid than diazepam, but not so, when compared with thiopentone. Midazolam decreases the anaesthetic requirement of inhalational agents.

CARDIOVASCULAR SYSTEM:

Midazolam decreases the myocardial contractility and systemic vascular resistance and causes vasodilatation,thus causing fall in arterial pressure. The fall in blood pressure is similar to that caused by hypnotic doses of thiopentone, greater than that caused by equipotent doses of diazepam and less than that caused by propofol. It increases the heart rate . Midazolam does not abolish the stress response to intubalion, but the increase in heart rate and blood pressure are less than seen with diazepam. Midazolam does not alter coronary vascular resistance and does not cause coronary steal phenomenon.

RESPIRATORY SYSTEM:

Midazolam causes dose dependent depression of ventilation. In doses used for premedication or sedation, it does not alter the carbondioxide response,but in doses above 0.2mg/kg it causes respiratory depression, Apnoea produced by midazolam is dose related and is more common in patients premeditated with opioids, in chronic obstructive pulmonary disorder patients, and following faster injection of the drug, Their respiratory depression is reversed by flumazenil but not by naloxone.

INTRATHECAL MIDAZOLAM:

Spinal midazolam produces analgesia by binding to specific benzodiazepine receptors in the dorsal horn of the spinal cord. Muscle relaxation is by potentiating the effect of glycine which is an inhibitory neurotransmitter to the anterior horn cells.

IN VITRO CHANGES IN TRANSPARENCY AND pH OF CSF CAUSED BY ADDING MIDAZOLAM:

CSF pH was decreased below 7.0 by adding more than 3mg of midazolam. CSF transparency was decreased by adding more than 7mg of midazolam. Midazolam in saline neither decreased the pH nor reduced the transparency. The pharmacokinetics of intrathecal midazolam depend on the molecular weight, lipid solubility and the systemic vascular absorbtion.

ANTAGONIST OF MIDAZOLAM:

Flumazenil is an imidazo benzodiazepine, with specific benzodiazepine antagonist activity. Flumazenil binds with high affinity to specific sites when it competitively antagonizes the binding and allosteric effects of benzodiazepine. The intravenous administration of 0.3 to 1mg of flumazenil is usually sufficient to abolish the effects of therapeutic doses of benzodiazepines within 1to2 minutes. Additional doses may be required after 1 to 2 hours.

USES OF MIDAZOLAM:

Premedication dose is 0.05 mg/kg to 0.1 mg/kg intramuscularly or 10-15 mg per oral. It has predictable absorption after intramuscular injection. It produces amnesia, anxiolysis and sedation .

1. Intravenous sedation dose is 0.05 mg/kg to 0.1mg/kg .Sedation occurs without loss of airway reflexes, causes no vomiting and post operative drowsiness is less.
2. Induction dose is 0.15mg/kg to 0.3mg/kg and induction is faster than with diazepam.
3. DAY CARE SURGERY: Because of rapid onset and brief half-life midazolam is a suitable drug. But patients should not drive vehicles for at least eight hours as midazolam affects

psychomotor function and postoperative instructions should be written down.

5. Midazolam can be used as treatment of emergence phenomenon

DRUG INTERACTIONS:

Erythromycin,clarithromycin and flucanozole increase the effect of midazolam due to inhibition of cytochrome P450 III A enzyme. H_2 receptor antagonist also inhibit cytochrome P450 III A enzyme. Asprin and probenecid increase the effect by competing for protein binding site. Phenytion, rifampicin and xanthines decrease the efficacy of midazolam due to increased metabolism by inducing cytochrome P 450.

SIDE EFFECTS:

Nausea and vomiting are minimal. Incidence of hiccough is 5.6%, cough is 1.5%.

MATERIALS AND METHODS

The study was conducted in 120 patients posted for elective surgeries after getting approval of ethical committee of department of Anaesthesiology, Government Rajaji Hospital and Madurai medical college,Madurai. Informed consent was obtained after explaining the procedure.

INCLUSION CRITERIA:

- Adult patients aged 20 – 55 yrs
- ASA physical status I and II
- Cases like lower abdominal surgeries and gynaecological surgeries

EXCLUSION CRITERIA:

- ASA physical status III and IV.
- Allergy to local anaesthetics .
- patients who were converted to general anaesthesia.

Palients are grouped into three groups Group B, Group M and Group F. Each group has 40 patients. All the patients received injection Atropine 0.6 mg intramuscularly 45 minutes before

induction.

Group B – received 15mg of 0.5% hyperbaric bupivacaine and 0.5ml of 0.9% sodium chloride solution.

Group M - received 15mg of 0.5% hyperbaric bupivacaine and 1mg (0.2ml)of preservative free midazolam and 0.3 ml of 0.9% Sodium chloride solution.

Group F – received 15 mg of 0.5 hyperbaric bupivacaine and 25mcg (0.5ml) of fentanyl .

Total drug volume in all the three groups is 3.5ml

PROCEDURE:

Patients were explained about the procedure

Base line pulse rate, blood pressure and respiratony rate were recorded.

Intravenous line was secured with 18 G canula.Preloading was done with 15- 20ml / kg of crystalloid solution. The following emergency drugs and equipment were kept ready.

- Boyle`s anaesthetic machine with oxygen cylinder.
- Laryrgoscope with varied blades
- Oropharyngeal airway.

- Endotracheal tubes
- Suction apparatus
- Drugs like atropine, adrenaline, ephedrine, dexamethasone, deriphylline, dopamine and naloxone.

Patients were put on right lateral position, under strict aseptic precaution. Subarachnoid block was performed using 23G Quinke Babcock`s needle in L3 – L4 interspaces. After ensuring free flow of CSF the drug was injected as per the group assigned. After injecting the drug patients were turned supine.

RECORDING DATA:

The following were recorded

1. Time of institution of subarachnoid block
2. Maximum level of sensory block achieved (which is tested by pinprick)
3. Time of onset of the maximum level of sensory block
4. Time of onset of the of surgery
5. Pulse rate, blood pressure, respiratory rate and oxygen saturation were monitored every 5 minutes for the first 15 minutes, threreafter every 10 minutes for rest of the surgery and every half an hour in the post operative period.

6. Hypotension was said to have occurred, if there was a fall in blood pressure 30% from the baseline. This was treated with 100% oxygen through face mask, intravenous fluids and ephedrine in titrated doses.
7. Discomfort, if any, experienced by the patient during surgery was recorded in the intraoperative period by sedation scale.

SEDATION SCALE

i. Patient awake anxious and agitated
ii. Patient awake oriented and tranquil
iii. Patient asleep but responds to commands only
iv. Patient asleep but responds briskly to light glabellor tap or loud auditory stimuli.
v. patient asleep but responds sluggishly to light glabellor tap or loud auditory stimuli.
vi. Patient asleep with no response to stimuli.

8. Occurence of pruritus was noted
9. Two segment regression time (i.e) the time taken to decrease from maximum sensory level by two segment from the initial level noted.

10.**ANALGESIA:**

Pain in the post oprative period was evaluated using word category scale

Contant worst pain	4
Severe pain	3
Moderate pain	2
Mild pain	1
No pain	0

Supplementary analgesia was given if the patient developed moderate pain during the post operative period. The duration of analgesia was taken as the time between the institution of subarachnoid block and analgesic requirement.

11. In the post operative period patients were followed up for any complication like respiratory depression,post operative nausea and vomiting.

The statistical significance was brought by student t test .

OBSERVATION AND RESULTS

The following observations were made during the intraoperative and post operative period.

DEMOGRAPHIC DATA:

The three study groups were compared with respect to age, weight, baseline vital parameters and duration of surgery .

DEMOTGRAPHIC DATA

SL.No.	Groups	Age (in years)	Base line	
			PR (perm in)	Bp (mm Hg)
1.	B	42.95 ±8.86	87± 4.89	118.25/ 75.75± 18.23 / 5.04
2.	M	41.48± 9.77	87.58± 5.44	119.5 /75.5 ±7.68 / 5.06
3.	F	38.01± 10.02	93.00± 5.4	118.3/78.7± 8.39/5.05

HIGHEST DERMATOME LEVEL ACHIEVED :

The maximum level of sensory block achieved was elicited with pinprick. The maximum level achieved in each group was:

Group 'B' : No patients had sensory block up to T_4 and T_5

10% of patients had sensory block up to T_6

37.5% of patients had sensory block up to T_7

40% of patients had sensory block up to T_8

75% of patients had sensory block up to T_9

5% of patients had sensory block up to T_{10}

Group M : 5% of patients had sensory block up to T_4

7.5% of patients had sensory block up to T_5

32.5% of patients had sensory block up to T_6

25% of patients had sensory block up to T_7

20% of patients had sensory block up to T_8

5% of patients had sensory block up to T_9

5% of patients had sensory block up to T_{10}

Group F : 30% of patients had sensory block up toT_4

25% of patients had sensory block up to T_5

22.5% of patients had sensory block up to T_6

12.5% of patients had sensory block up to T_7

5% of patients had sensory block up to T_8

No patients had sensory block up to T_9 and T_{10}

TIME OF ONSET:

The time taken to reach the maximum sensory block was as follows

Group B : 7.35 Mins ± 1.33

Group M : 4.55 Mins ± 1.28

Group F : 4.03 Mins ± 0.97

TWO SEGMENT REGRESSION TIME:

The average two segment regression time in each group was

Group B : 96.28 Mins ± 17.84

Group M : 141.63 Mins ± 15.87

Group F : 190.75 Mins ± 18.18

DURATION OF ANALGESIA:

The mean deviation of analgesia was

Group B : 145.55 Mins ± 16.69

Group M : 195.08 Mins ± 19.72

Group F : 253.63 Mins ± 26.79

INCIDENCE OF SIDE EFFECTS:

HYPOTENSION:

The incidence of hypotension and vasopressor requirement in each group was.

Group B : 10% of patients got hypotension

Group M : 10% of Patients got hypotension

Group F : 20% of Patients got hypotension

BRADYCARDIA:

The incidence of bradycardia (ie. pulse rate less than 60 per minute)

Group B : 5% of Patients got bradycardia

Group M : 2.5% of Patients got bradycardia

Group F : 10% of Patients got bradycardia

RESPIRATORY DEPRESSION:

Respiratory depression is set to have occurred if respiratory rate was less than 10 per minute. One patient in Group F had respiratory depression and required oxygen supplementation.

SEDATION SCALE:

The sedation scale for each group was

Group B 10% of patients had sedation score of 1

75% of patients had sedation score of 2

15% of patients had sedation score of 3

Group M 12.5% of patients had sedation score of 2

47.5% of patients had sedation score of 3

40% of patients had sedation score of 4

Group F Only 5% of patients had sedation score of 2

37.5% of patients had sedation score of 3

52.5% of patients had sedation score of 4

50% of patients had sedation score of 5.

DISCUSSION

The international Association and Society for Pain (IASP) defines pain as “An unpleasant sensation and emotional experience associated with actual or potential tissue damage or described in terms of such damage”.

It has also been defined by Sherington in 1906 as “The physical adjunct of protective reflex”.

Opioids have been used for pain relief since time immemorial and are still considered the gold standard analgesic medication. The advances in pain relief with opioids includes the discovery of newer drugs and the use of various routes of administration of the drug. In addition to the conventional oral, sublingual, intramuscular and intravenous routes opioids and benzodiazepines are also administered into the central neuraxis. The neuraxial adjuvants like opioids and benzodiazepines are becoming increasingly popular because of their prolonged duration of action, minimal incidence of side effects and good intraoperative comfort.

Spinal anesthesia continues to be the commonly used anesthetic technique in our country. Hence the addition of the adjuvants to the local anaesthetic becomes easier.

Among the opioids, lipophilic drugs are safer within the central neuraxis as their cephalad spread is restricted. On administration into the CSF, the opioid gets attached to the spinal cord opioid receptor and produce their effect. Among the benzodiazepines, only the midazolam is used within central neuraxis. It produces analgesia by binding to the specific benzodiazepine receptor in the dorsal horn of the spinal cord.

This is the study to evaluate and compare the intrathecally administered fentanyl and midazolam in their post operative analgesia and intraoperative comfort.

Major advantages have been observed with four parameters.

1. Time of onset:

The time required to achieve the maximum level of block has been shortened with the addition of midazolam and fentanyl but more so with fentanyl. The p value for time of onset is found to be.

0.000001 on comparing group B and group M

0.000001 on comparing group B and group F

0.0439 on comparing group M and group F

Since p value is less than 0.05, this faster onset of action is found to be statistically significant.

2. Two segment regression time:

The two segment regression time is prolonged in both adjuvant groups compared with the control group in a statistically significant manner. The p value for two segment regression time is found to be.

0.00001 on comparing group B and group M

0. 0000001 on comparing group B and group F

0. 000001 on comparing group M and group F

3. Duration of analgesia:

Duration of analgesia has been shown to be prolonged with the addition of the midazolam and fentanyl. Fentanyl scores over midazolam in duration of analgesia in a statistically

significant manner. The p value has been found to be

0.00001 on comparing group B and group M

0.0000001 on comparing group B and group F

0. 000001 on comparing group M and group F

Groups	**Time of onset (Minutes)**	**Two segment regression time (Minutes)**	**Duration of analgesia (Minutes)**
B	7.35 + 1.33	96.28 + 17.84	145.55 + 16.69
M	4.55 + 1.28	141.63 + 15.87	195.08 + 19.72
F	4.03 + 0.97	190.75 + 18.18	253.63 + 26.79
Comparison			
B and M t p	9.5396 0.000001	12.0122 0.000001	12.1253 0.00001
B and F t p	12.7556 0.000001	23.4572 0.000001	21.6565 0.0000001
M and F t p	2.0475 0.0439	12.8733 0.000001	11.1318 0.000001

INTRAOPERATIVE COMFORT:

Intraoperative comfort here denotes mainly the absence of discomfort during manipulation of viscera (uterus & bowel) and patient sedation.

On comparing sedation level intraoperatively with midazolam and fentanyl, they are statistically significant. p value on comparing group M and group F is 0.0261 which is significant. This shows that patients who received fentanyl were more comfortable than those of midazolam group.

SIDE EFFECTS:

On comparing fentanyl and midazolam with respect to their side effects like hypotension, bradycardia and respiratory depression, the incidence of hypotension and bradycardia is 2 times more with fentanyl group than with midazolam group and one patient got respirtory depression in fentanyl group which was not present in midazolam group. Pruritus was not reported in any case.

So midazolam group patients were hemodynamically stable compared with fentanyl.

CONCLUSION

From this study comparing the midazolam and fentanyl in intrathecal administration shows that

- The addition of fentanyl and midazolam gives better intraoperative comfort and post operative analgesia than local anaesthetic bupivacaine. But the fentanyl gives more comfort and prolonged duration of analgesia than midazolam.
- The midazolam gives more hemodynamic stability than fentanyl group, by less incidence of hypotesion and bradycardia.
- The sedation without desaturation is a welcome effect in the immediate post operative period with midazolam.

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PROFORMA

COMPARATIVE STUDY OF INTRATHECAL MIDAZOLAM WITH INTRATHECAL FENTANYL IN COMBINATION WITH BUPIVACAINE

NAME: **AGE/SEX**: IP NO.: DATE:

WEIGHT: **ASA RISK**:

DIAGNOSIS:

GROUP M 1mg Midazolam+3ml Bupivacaine+0.3ml 0.9%Nacl

GROUP B 3ml Bupivacaine+0.5ml 0.9%Nacl

GROUP F 25microgm Fentanyl+3ml Bupivacaine

Time of Spinal block:

Space of Spinal block:

Needle type & size:

Composition of drug:

Onset of spinal block (pinprick): (0) Normal sensation

(+) pinprick recognized as touch

(++) no perception of touch

Level of Spinal block (pinprick):
(max. level by no perception of touch

Time of Starting of Surgery :

Baseline : Pulserate : Blood Pressure :

Monitoring: every 5 mins for 15 mins then every 10 mins for rest of surgery

TIME	HR	BP	RR	SpO2

Duration of Surgery:

Time of 2 segment regression of spinal block:

Postoperative follow up - Duration of absolute postoperative analgesia:

TIME	RR	WCS	LEVEL OF SB	SEDATION	RESIDUAL ANALGESIA

WORD CATEGORY SCALE

CONSTANT PAIN	4
SEVERE PAIN	3
MODERATE PAIN	2
MILD PAIN	1
NO PAIN	0

SEDATION SCALE

1. awake,anxious,agitated
2. awake,oriented,tranquil
3. awake but responds to commands only
4. asleep but responds briskly to light glabellar tap or loud auditory stimuli
5. asleep but responds sluggishly to light glabellar tap or loud auditory stimuli
6. asleep no response to stimuli

GROUP B													
S. No	Age	Sex	Time of onset of sensory block (mins)	Height of block	PR (/min)	Systolic BP (mmHg)	Diastolic BP(mmHg)	RR (/min)	SPo2 (%)	Sedation scale	2 Seg. regression time (mins)	Duration of analgesia (mins)	Complication
1	43	M	6	8	66	110	60	16	99	2	105	155	nil
2	28	M	7	7	70	110	60	14	99	2	95	148	nil
3	36	F	5	7	70	93	56	16	98	2	88	143	Hypotension
4	53	M	6	9	70	100	70	16	98	3	102	136	Nil
5	55	M	9	7	58	100	60	14	94	3	130	184	Nil
6	45	M	5	8	67	100	60	16	94	2	100	135	Nil
7	54	F	6	8	80	100	70	16	98	2	75	142	Nil
8	39	M	7	10	90	110	70	16	99	1	64	120	Nil
9	41	F	5	8	90	100	60	14	98	2	108	142	Nil
10	48	F	6	8	80	110	60	16	99	2	124	165	Nil
11	44	F	7	6	62	90	50	14	98	2	108	160	Nil
12	52	M	7	7	72	104	54	14	96	1	72	108	Hypotension
13	53	F	7	7	70	108	60	14	94	2	120	152	nil
14	28	F	7	8	70	100	60	14	98	2	96	140	nil
15	32	M	8	7	84	110	60	18	98	3	98	140	nil
16	42	F	7	7	66	100	60	14	98	2	92	145	nil
17	46	M	6	9	80	100	60	16	96	2	105	145	nil
18	34	M	7	6	70	120	60	18	96	2	100	165	nil
19	36	M	7	7	76	120	60	16	98	2	155	140	nil
20	32	M	7	7	80	100	60	16	96	2	90	135	nil
21	39	F	8	8	90	104	60	14	96	2	75	120	nil
22	46	F	9	8	92	106	56	14	96	2	100	160	nil
23	40	F	6	8	74	100	70	16	97	2	110	165	nil
24	55	F	9	9	60	120	60	26	94	1	70	105	nil
25	54	F	9	7	72	80	56	16	94	2	105	150	Hypotension
26	38	F	7	7	74	90	60	14	97	2	100	140	nil
27	53	M	6	8	74	98	60	16	99	2	75	145	nil
28	55	F	8	7	60	110	60	16	98	3	85	140	nil
29	46	F	10	8	58	110	60	16	96	3	95	160	bradycardia
30	47	M	8	8	64	104	60	16	98	2	105	155	nil
31	41	M	8	8	72	100	60	16	96	2	75	150	nil
32	38	F	9	7	80	120	60	18	98	2	90	145	nil
33	40	F	7	6	54	90	60	14	96	2	82	130	bradycardia
34	46	M	8	6	64	84	55	16	98	2	106	180	Hypotension
35	54	M	8	8	80	100	80	16	96	2	96	165	nil

36	53	F	10	8	82	100	70	14	95	3	75	132	nil
37	48	F	10	10	90	110	70	14	99	2	80	160	nil
38	32	F	8	8	72	100	70	16	98	2	105	140	nil
39	26	M	7	7	74	100	60	18	98	1	90	130	nil
40	26	M	7	7	62	110	70	16	96	2	105	150	nil

GROUP M													
S. No	Age	Sex	Time of onset of sensory block(mins)	Height of block	PR (/min)	Systolic BP (mmHg)	Diastolic BP(mmHg)	RR (/min)	SPo2	Sedation scale	2 Seg. regression time (mins)	Duration of analgesia (mins)	Complication
1	50	M	3	6	80	100	80	12	99	3	110	190	nil
2	55	M	3	7	76	100	60	14	98	3	135	190	nil
3	32	M	4	8	76	90	54	12	96	3	140	205	nil
4	51	F	3	7	95	90	54	16	96	2	140	195	nil
5	29	M	8	8	96	100	80	16	98	3	120	225	nil
6	35	F	5	10	92	110	80	16	98	2	100	180	nil
7	55	M	6	7	76	110	80	16	99	2	125	205	nil
8	37	M	4	9	80	100	70	16	98	2	140	225	nil
9	42	F	4	10	90	110	70	16	99	2	120	200	nil
10	45	F	3	9	90	100	60	16	98	3	140	190	nil
11	36	F	5	8	84	100	70	16	98	2	125	205	nil
12	28	F	5	6	50	100	64	12	92	3	145	190	Bradycardia
13	27	M	4	8	64	100	62	10	94	4	160	205	nil
14	52	M	5	6	64	84	54	10	96	4	165	225	Hypotension
15	46	F	5	7	68	90	60	14	96	3	170	220	nil
16	44	F	5	6	72	94	62	14	96	3	135	225	nil
17	31	F	3	8	70	98	60	12	98	3	145	200	nil
18	32	F	4	6	60	100	90	14	98	3	150	198	nil
19	45	M	4	4	58	94	62	12	94	4	135	190	nil
20	54	M	5	5	60	90	60	10	92	4	130	225	Respiratory depression
21	52	M	5	6	72	84	54	12	96	4	135	180	Hypotension
22	28	F	4	4	76	96	60	12	98	4	140	185	nil
23	29	F	3	7	90	100	60	14	98	3	160	180	nil
24	46	F	6	8	88	100	70	14	96	3	155	200	nil
25	47	M	3	6	80	90	60	16	98	4	165	190	nil
26	33	M	4	5	90	110	90	14	97	4	135	180	nil
27	46	F	5	7	64	100	60	14	98	3	145	200	nil
28	48	F	4	6	68	104	64	14	97	4	130	165	nil
29	54	F	4	6	80	100	60	14	96	4	145	190	nil
30	51	F	4	6	86	110	60	14	97	3	145	175	nil
31	53	M	5	7	90	120	60	12	96	3	125	180	nil
32	42	F	8	6	70	110	60	14	97	4	145	205	nil
33	26	M	6	5	76	80	46	12	98	4	155	190	Hypotension
34	28	M	6	6	82	84	64	12	96	4	150	190	Hypotension
35	29	M	7	7	90	100	70	12	98	3	160	205	nil

36	42	M	4	8	80	110	70	12	96	3	130	180	nil
37	41	M	4	7	70	100	60	12	97	4	150	215	nil
38	52	M	3	7	80	100	60	10	96	3	175	205	nil
39	54	F	4	8	88	110	70	12	98	3	145	120	nil
40	32	F	5	6	90	90	60	12	97	4	145	180	nil

GROUP F													
S. No	Age	Sex	Time of onset of sensory block (mins)	Height of sensory block	PR(/min)	Systolic BP (mmHg)	Diastolic BP(mmHg)	RR (/min)	SPo2 (%)	Sedation scale	2 Seg. regression time (mins)	Duration of analgesia (mins)	Complication
1	42	F	3	5	60	100	65	12	96	4	190	240	nil
2	35	F	4	4	70	90	60	14	96	4	115	230	nil
3	27	F	4	6	80	98	71	14	96	4	105	255	nil
4	45	M	4	4	64	90	70	10	92	5	195	285	Respiratory depression
5	52	M	3	5	60	80	54	12	94	4	190	260	Hypotension
6	26	M	4	6	70	98	60	14	96	3	198	240	nil
7	41	F	3	4	72	100	60	12	94	3	208	250	nil
8	38	F	5	5	76	100	64	12	98	4	200	265	nil
9	54	M	5	7	70	100	60	12	99	4	180	240	nil
10	56	F	6	7	84	90	60	12	96	2	185	225	nil
11	42	F	3	6	50	100	60	12	92	4	225	310	Bradycardia
12	36	M	4	6	70	90	60	14	94	3	195	245	nil
13	37	M	4	8	80	100	60	14	98	3	220	265	nil
14	27	M	3	7	68	110	70	14	96	2	124	230	nil
15	24	M	3	6	64	88	54	12	96	4	190	250	Hypotension
16	28	F	3	4	50	90	60	12	92	4	195	270	Bradycardia, Hypotension
17	32	M	5	5	60	90	60	8	88	5	220	295	respiratory depression
18	42	F	3	5	64	100	60	18	98	4	180	250	nil
19	51	F	4	6	66	90	60	12	96	3	190	235	Hypotension
20	38	F	4	6	70	94	64	12	99	3	195	225	nil
21	46	F	4	6	74	96	68	14	96	4	225	270	nil
22	55	M	6	5	90	90	54	14	96	4	220	280	Hypotension
23	25	M	6	4	92	100	60	12	90	3	230	270	nil
24	31	F	5	4	70	110	60	12	96	3	190	240	nil
25	29	F	5	4	74	100	60	12	94	3	180	250	Hypotension
26	26	M	5	5	88	92	60	14	94	3	165	195	Hypotension
27	36	M	5	5	92	92	60	14	99	4	200	270	nil
28	34	M	4	4	90	100	60	10	97	4	210	310	nil
29	33	M	4	4	70	110	70	12	96	4	225	315	nil
30	28	M	3	6	74	100	64	14	99	4	190	260	nil
31	45	F	3	8	80	110	70	16	100	3	150	200	nil
32	50	M	4	7	60	110	70	14	100	3	200	250	nil
33	55	M	3	6	50	100	64	14	99	3	215	265	Bradycardia

34	52	M	4	7	60	100	64	16	100	3	200	240	nil
35	53	F	6	4	50	88	54	12	96	4	215	250	Bradycardia, Hypotension
36	33	F	3	5	70	100	58	14	98	4	190	270	nil
37	31	F	3	6	72	100	70	16	98	3	190	260	nil
38	28	M	3	4	72	100	60	16	96	4	180	220	nil
39	29	M	4	5	70	100	60	14	96	4	190	240	nil
40	32	M	4	4	80	94	60	12	96	4	165	225	nil